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Review

Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations

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ABSTRACT

Antiepileptic drugs (AEDs) and hormonal contraceptives may affect each other's metabolism and clinical efficacy. Loss of seizure control and unplanned pregnancy may occur when these compounds are used concomitantly. Although a large number of available preparations yield a plethora of possible drug combinations, most of these drug interactions are predictable and, thus, avoidable.

Unfortunately, there is a substantial lack of data regarding the newer AEDs. Detailed understanding of these issues is necessary for those who prescribe AEDs and/or hormonal contraception to women with epilepsy, as well as for those who provide comprehensive care, education and counseling to them, in order to reduce the unacceptably high number of unplanned pregnancies among women with epilepsy.

1. Introduction

Patients using antiepileptic drugs (AEDs) face unique challenges regarding hormonal contraception. Combined oral contraceptives (COCs) and AEDs can interact bi-directionally, resulting in possible therapeutic failure of either treatment, which may lead to unintended pregnancy and/or increased seizure activity. Contraceptive failure is a disaster for all women, but is particularly critical for women with epilepsy (WWE) owing to the teratogenic potential of the AEDs and other adverse effects on the developing child [1,2]. Unfortunately, contraceptive failure in women using AEDs is disturbingly common [3].

Treating WWE of fertile age includes systematic, ongoing and accurate counseling to find the optimal method of contraception. The wide range of available AEDs and hormonal contraceptive methods underlines the importance of being familiar with the various pharmacokinetic properties of the drugs to achieve a better understanding of potential drug–drug interactions. However, several surveys suggest that health care professionals often have limited knowledge on potential interactions between AEDs and hormonal contraception [3,4], and a significant number of WWE who take COCs deny to have ever received information about this specific issue [5–8]. It has also been shown that these women do not always recall being given such information. This highlights the need for regular, repeated counseling so they can make informed choices [9].

When used properly, the oral contraceptive (OC) failure rate is 1% in healthy women, but 3–6% in WWE [10,11]. One study demonstrated that less than 55% of WWE had planned their pregnancy and OC failure was the cause of one in four unplanned pregnancies [12].

Taking into account all of the above and the fact that AEDs are not only used for the treatment of epilepsy but also for other, even more frequent indications such as neuropathic pain, general anxiety disorders, migraine and bipolar disorder, it is obvious that physicians and other health care providers should have adequate knowledge of possible interactions between hormonal contraception and AEDs.

2. Types of hormonal contraception

An increasing number of different hormonal contraceptives have been introduced during the past decades (Table 1).

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Table 1
Types of hormonal contraception.

Type	Active ingredient	Route of administration
Combined oral contraceptive (COC) ("*the pill*")	Estrogen + progestin	Orally
Combined dermal patch	Estrogen + progestin	Transdermally
Vaginal ring	Estrogen + progestin	Intravaginally
Progestin-only pills ("*mini-pill*" and "*morning-after pill*")	Progestin	Orally
Progestin-only implants	Progestin	Subdermally
Progestin-only depot injections	Progestin	Intramuscularly
Progestin-only intrauterine device	Progestin	Intrauterine device

2.1. Combined hormonal contraception

Despite concerns regarding adverse cardiovascular and neoplastic effects, combined estrogen and progestin contraceptives (COCs) are among the most widely used contraceptive agents [13,14]. COCs ("the pill") traditionally contain a combination of a synthetic estrogen and a progestin. The composition in terms of type and dose of the estrogen and progestin constituent has changed considerably over time. While the oldest COCs contained up to 150 μg estrogen (in the form of mestranol, a pro-drug of ethinyl estradiol), subsequent preparations used gradually decreasing amounts of estrogen, in order to minimize the risk of venous thrombosis, cardiovascular disease and other adverse effects. The most recent agents contain only 20–35 μg ethinyl estradiol (EE), the most commonly used estrogen used in COCs. The dose of EE in these agents is too low to ensure suppression of ovulation and serves mainly to provide proper cycle control, whereas the progestin component is responsible for the contraceptive mechanisms which include inhibition of ovulation as well as increased viscosity of the cervical mucus and reduced endometrial suitability for ovum implantation [15]. Recently, a new class of COC was introduced, containing estradiol valerate (a prodrug of estradiol) and dienogest, a progestin, both dosed in the 2–3 mg range. Several benefits have been suggested for this COC, including reduction of strong menstrual bleeding and fewer hormone-withdrawal symptoms [16].

Progestins are synthetic progestogens with a molecular structure similar to endogenous progesterone, but their steroid skeleton has been provided with different substituents to enhance bioavailability, modify their molecular actions, and to prolong their half-life [17]. The oldest progestin compound used in COCs, norethynodrel, was chemically related to nortestosterone and was associated with undesirable androgenic effects. Today, a large number of progestins are used in COCs, including norethindrone, levonorgestrel, norgestimate, norgestrel, desogestrel, and drospirenone. Still, some of them are chemically classified as nortestosterone derivatives. Progestins may show both weak androgenic and antiandrogenic effects, depending on their structure and receptor affinity. Some progestins are prodrugs and show progestogenic effects only after bioactivation [17].

An ordinary COC is usually taken once daily for 21 days followed by a seven days pause ("pill-free week") during which withdrawal bleeding occurs, in order to mimic a menstrual cycle. Extended-cycle regimens, e.g. 84 days with a 7-day gap, have been suggested and seem to be safe and well-tolerated [18]. Even longer periods of continuous intake (up to one year) have been reported in smaller studies and case reports [19].

In addition to COCs, skin patches and vaginal rings which contain an estrogen and a progestin are available. While the skin patch releases the hormones into the systemic circulation and induces suppression of ovulation, the vaginal ring acts predominantly locally.

2.2. Progestin-only methods

Progestin-only methods include the progestin-only pill ("mini pill", POP) as well as subcutaneous progestin implants, progestin-releasing intrauterine devices (IUDs) and intramuscular depot injections. The site of action of these methods varies and depends not only on the mode of administration, but also on the dose. Low-dose oral compounds act locally on the endometrium and by decreasing tube-motility, while the higher-dosed oral preparations as well as the subdermal and intramuscular methods act mainly by suppression of ovulation [20].

2.3. Emergency contraception

Emergency contraceptives ("morning-after pill") are progestin-only tablets and must be taken as soon as possible after unprotected sexual intercourse. The progestin used in the vast majority of these agents is levonorgestrel, but in a higher dose as in ordinary POPs.

2.4. Metabolism of hormonal contraceptives

The estrogen compound used in virtually all combined hormonal contraceptive methods is 17-α-ethinyl estradiol (EE). The newly introduced estradiol valerate is a prodrug and biotransformed to the naturally occurring estradiol [21]. EE is extensively metabolized and subject to significant first pass metabolism. More than 30% of the dose undergoes gut wall metabolism, mainly by sulfotransferase (SULT) dependent conjugation [22]. Its further biotransformation is catalyzed by cytochrome P450 (CYP), uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 and SULT. All these enzymes can serve as a site of metabolic drug–drug interactions. Most of EE is hydroxylated to inactive metabolites, catalyzed predominantly by CYP3A4. Also CYP2C9, CYP2C8, CYP2C19, and CYP3A5 are contributing but play a minor role [23]. The hydroxylated metabolites then undergo conjugation by UGT and SULT and are subject to enterohepatic re-circulation.

Glucuronidation is inhibited by valproate, and induced by phenobarbital, phenytoin and other enzyme inducing drugs. EE itself may induce UGT enzymes, thereby affecting the metabolism of drugs principally metabolized by this route such as lamotrigine or paracetamol. Moreover, it has long been known, although not widely acknowledged, that EE is a moderate inhibitor of various CYP enzymes and can increase the serum concentrations of many other drugs significantly [24,25].

Similar to EE, the metabolism of progestins also involves CYP-mediated hydroxylation, reduction, deacetylation, and subsequent sulfatation (via SULT) and glucuronidation (via UGT) [17].

2.5. Specific drug–drug interactions

Previous studies and recommendations on the interaction between hormonal contraceptives and AEDs have mainly focused on the alteration of the estrogen component of the agents. However, due to the ever-decreasing estrogen content in modern COCs, it is now in fact the progestin component that provides the major part of the contraceptive effect of modern COCs [15,20]. Thus, the progestin component in modern COCs should be in the spotlight of future studies on drug interactions with modern hormonal contraceptives. Moreover, the example of lamotrigine has brought to our minds that hormonal contraceptives may interfere with the metabolism of AEDs and affect their clinical efficacy [26].

Table 2
Bi-directional drug interactions between hormonal contraceptives and antiepileptic drugs.

	AED may be reduced by COC	Ethinyl estradiol may be reduced by AED	Progestin may be reduced by AED	References
Carbamazepine	n.a.	Yes	Yes	[24,28]
Eslicarbazepine	n.a.	Yes	Yes	[35]
Felbamate	n.a.	Yes	Yes	[31]
Gabapentin	n.a.	No	No	[38]
Lacosamide	no	No	No	[42]
Lamotrigine	Yes	No	Yes	[26,43,52]
Levetiracetam	No	No	No	[39,45]
Oxcarbazepine	n.a.	Yes	Yes	[34]
Perampanel	n.a.	No	Yes[a]	[36]
Phenobarbital	n.a.	Yes	Yes	[24,53]
Phenytoin	n.a.	Yes	Yes	[24,28,51]
Pregabalin	n.a.	n.a.	n.a.	
Retigabine/ezogabine	No	No	No	[48]
Rufinamide	No	Yes	Yes	[54]
Stiripentol	n.a.	n.a.	n.a.	
Topiramate	n.a.	Yes[a]	No	[32,33]
Valproate	Yes	No	No	[37,44,45]
Zonisamide	No	No	No	[40,41]

COV: combined oral contraceptive; n.a.: no data available.
[a] dose dependent.

Carbamazepine, phenobarbital, and phenytoin are potent enzyme inducers and can accelerate the metabolism of hormonal contraceptives, thus increasing the risk of unplanned pregnancy, see Table 2 [24,27,28]. These AEDs have also been shown to increase the amount of sexual hormone binding globulin (SHBG) in the blood [29,30]. With increased SHBG, the free, biologically active proportion of endogenous and exogenous sexual steroid hormones decreases.

Felbamate [31] and topiramate [32,33] are less potent inducers and may alter plasma concentrations of hormonal contraceptives to a lesser degree. Oxcarbazepine also has a lower potential to enzyme induction, but unfortunately exerts a similar effect on hormonal contraceptives as carbamazepine [34]. Eslicarbazepine is the S-enantiomer of the active constituent of oxcarbazepine and does also reduce the plasma concentrations of EE and progestins [35]. As it is generally used with lower serum concentrations than the racemic mother compound, the interaction effect might theoretically be lower than for oxcarbazepine.

With some AEDs, the extent of enzyme induction may be dose-dependent, but this is difficult to quantify and subject to great inter-individual variation. This can be exemplified by topiramate which in monotherapy at dosages less than 200 mg did not significantly affect the pharmacokinetics of combined COCs containing 35 μg EE [32]. Thus, COCs containing 35 μg ethinyl estradiol might remain sufficiently active in women receiving low dose topiramate monotherapy. This is an important finding, as many fertile women use low dose topiramate, particularly in migraine prophylaxis. A selective, dose dependent induction of progestin metabolism has been demonstrated for perampanel, an effect thought to be clinically significant at 12 mg [36]. It has not yet been studied to what extent low dose POPs (“mini-pills”) may be vulnerable at lower perampanel doses.

For all enzyme inducing AEDs it has generally been suggested that women who are taking these AEDs use high-dose COCs, but this advice is not evidence based. In fact, the first reports on contraceptive failure in WWE using enzyme inducing AEDs were published in the 1970s, when COCs contained considerably higher EE doses than today’s COCs. The additional use of barrier methods of contraception is therefore also recommended [20].

Available data, although sparse, suggest that neither valproate [37], gabapentin [38], levetiracetam [39], zonisamide [40,41], nor lacosamide [42] affect the metabolism of COCs. These AEDs may therefore be regarded as safe with respect to possible contraceptive failure. Lamotrigine, however, may have a modest decreasing effect on the plasma level of the levonorgestrel [43] while the EE compound is not affected. When interpreting these data it is important to consider that the women in these studies were taking moderate-dose COCs that contained 35 μg EE plus 150 μg levonorgestrel. It cannot be ruled out that the contraceptive effect of low-dose COCs that contain less than 30 μg EE and only 75 μg progestin or low dose POPs may be impaired by lamotrigine. Therefore, midcycle bleeding should always alert the physician and the patient to the risk of contraceptive failure.

While some AEDs may induce the metabolism of EE and progestins, EE itself may affect the metabolism and serum concentrations of other drugs through inhibition of CYP enzymes and by induction of UGT enzymes. Thus, the metabolism of AEDs may be affected by hormonal contraceptives. Indeed, both lamotrigine and valproate serum concentrations are reduced when EE is taken concomitantly [26,44,45], presumably due to accelerated glucuronidation. The clinical relevance of the modest effect on valproate is unclear. However, lamotrigine serum concentrations may decrease by more than 50%, and therapeutic failure in the form of increased seizure frequency/recurrence of seizures has been reported [26].

The effect of COCs on lamotrigine both establishes and vanishes within a few days after start and cessation of active EE treatment [43,46], suggesting that induction and de-induction of UGT occur much faster than seen with other metabolic pathways, such as cytochrome P450. In women using COCs in a common 28-day regimen, routine serum concentration measurements of lamotrigine should thus be performed while they are on day 7–21 of the new cycle, i.e. in pharmacokinetic steady-state of active EE treatment, and *not* during the *pill-free* week.

A study on the differential effects of EE and progestins suggested that progestin-only methods do not alter the lamotrigine serum concentrations, a finding which is of practical importance [47].

Licarbazine, the active monohydroxy metabolite of oxcarbazepine, and its S-enantiomer, eslicarbazepine, are also metabolized by UGT enzymes and may therefore be affected by EE, but this effect is difficult to study in a naturalistic setting, as these drugs are usually not combined with contraceptive pills.

A potential effect of hormonal contraception has been studied only for few other AEDs, namely levetiracetam, zonisamide, lacosamide and retigabine/ezogabine. The available data suggest that the metabolism of these AEDs is not affected [40–42,48,49].

To our knowledge, no specific drug interactions studies have been carried out with respect to estradiol valerate and AEDs. However, one study with postmenopausal WWE on hormone replacement therapy with conjugated equine estrogens showed that two subjects taking lamotrigine had a decrease in their lamotrigine levels of 25–30% [50]. Studies on the interaction potential of estradiol valerate are awaited.

Very few data about possible interactions between AEDs and progestin-only contraceptive methods are available. Enzyme-inducing AEDs increase the metabolism of progestins as well as of estrogens, and POPs should not be regarded as effective. It has also been shown that subdermal progestin implants do not provide reliable contraception in WWE using enzyme-inducing AEDs [51]. The authors are not aware of any specific studies on possible interactions between AEDs and the *morning-after pill*.

3. Conclusion

Millions of fertile women use AEDs and hormonal contraception concomitantly. There are a large number of available preparations and possible drug combinations, and the risk for bi-directional drug–drug interactions is high. Most of these interactions follow common patterns and mechanisms, which makes them predictable and, thus, avoidable. Regrettably, failure of either treatment, especially contraceptive failure resulting in unplanned pregnancy, occurs in an unacceptably high proportion of patients. Fertile women with epilepsy indeed need individually tailored treatment with consideration of birth control. Detailed understanding of these complex interactions is necessary for those who prescribe AEDs and/or hormonal contraception to WWE, as well as for those who provide comprehensive care, education and counseling including contraceptive advice to these patients. Given the magnitude of the problem and the general lack of data, health authorities should demand adequate testing of possible interactions with hormonal contraception before a new AED is granted marketing authorization. Future research in this field should focus at least as much on progestins as on estrogens.

Conflict of interest statement

None declared.

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